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EXAMINER
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,886	BIANCHI ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14 and 16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14 and 16-22* is/are rejected.

7)☒ Claim(s) *23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, and to a specific species of the invention in the replies filed on August 25 and December 13, 2005 is acknowledged. The elected species is represented by the peptide comprising positions F-E-D-C-B-A-A'-B'-C'-D', wherein F is aspartic acid, E is (d) Glutamic acid, D is Leucine, C is Isoleucine, B is β-cyclohexylalanine, A is Cysteine, B' is β-cyclohexylalanine, and C' is Aspartic acid. The traversal with respect to Group I and III is on the ground(s) that the Wang reference does not anticipate the indicated claims.

Because the claims now read on a composition and a first method of using such, the claims of Groups I and III are rejoined.

With respect to the species elections, the Applicant asserts that the various species may be used together. However, the different species of peptides still lack unity in that each of them represents a different peptide sequence, which is distinct from the other possible species within the generic formula. It is also noted that it is Office policy to permit only one sequence per application. Thus, the species election requirement is maintained.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-12, 14, and 16-23 are pending and under consideration.

Specification

3. The specification is objected to for referring to protein or nucleic acid sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). See, pages 14-16 and 17 (Tables 2 and 3), page 24 (lines 12-13), page 26 (lines 15-16), page 27 (line 6), pages 31-32 (Table 4), and page 34 (line 4). The examiner would like to bring the applicant's attention to the following excerpt from MPEP §2422.03:

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This

> requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO: 23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The applicant is therefore required to amend the specification to comply with 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12, 14, and 16-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to a genus of peptides (or methods of using such for the treatment of an HCV infection) having the formula Pep-A'-B'-C'-D', wherein Pep is any peptide or analog thereof that binds to HCV NS3 protease, or any such peptide or analog according to a formula presented in (e.g.) claims 11 and 12. Claim 1 identifies the residue of position A' as proline, but also indicates that this residue may optionally be substituted. Thus, A' may be any amino acid. Residues B', C', and D' are, respectively, identified as an amino acid or analog having a non-polar side chain, a polar side chain, or a residue (or peptide of 2-6 residues comprising at the N-

terminus a residue) that is leucine or other amino acid with a non-polar aliphatic side chain. The claims also require that the bond between the peptide elements Pep and A' "is substantially uncleavable by NCV NS3 protease." The claims are therefore drawn to a genus of peptides according to the formula provided above, wherein A' can be any amino acid and Pep can be any peptide, or a peptide according the indicated formulas, and wherein the bond between Pep and A' is substantially uncleavable by NS3.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed. However, it may also be found where the genus is identified through a combination of a function, and a non-functional characteristic that correlates to the presence of that function.

In the present case, the application has provided several examples of peptides with some level of NS3 inhibiting activity. See e.g., pages 31-32 (Table 4- peptides 1, 2, and 10-30 of

which appear to fall within the scope of claim 1- the broadest claim). However, review of this table demonstrates that each of these peptides, with two exceptions (peptides 3 and 6- neither of which is within the scope of claim 1), comprises either a proline or an N-methylated alanine residue in position A'. Each of the embodiments corresponding to the elected species comprises a proline in this position. In view of the fact that each of the disclosed operative species of the claimed peptides have one of three residues in the A' position, and proline is disclosed for the elected embodiments, these disclosed species are insufficient to demonstrate possession of the full scope of the genus which can comprise any amino acid in this position.

It is noted that the art appears to recognize that substitution of residues corresponding to position A' (position P_1' or P1') in NS3 cleavage substrate peptides with a proline results in the inability of the enzyme to perform its protease activity on the peptide. See e.g., Kolykhalov et al., J Virol 68: 7525-33 (esp., pages 7527-right column, and 7531-left column); and Landro et al., Biochem 36: 9340-48, at 9343 right column. Thus, there would appear to be a recognition in the art between the required inhibitory function of the peptides, and the presence of a proline in position A'.

The claims are not however limited to embodiments wherein residue A' is a proline. Further, the Federal Circuit has determined that the presence of multiple species with in a claimed genus does not necessarily demonstrate possession of the genus "where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated." See e.g., In re Smyth, 178 U.S.P.Q. 279 at 284-85 (CCPA 1973); and University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1405 (Fed Cir 1997)(citing Smyth for support). In the present case, while it appears that a proline at position A' corresponds

to inhibitory activity, there is no demonstration that this result is universal to any substitution of the A' position.

The teachings of the application in combination with those of the art indicate that modifications of other positions may also result in peptides meeting the functional requirements of the claims. For example, as was indicated above, the application discloses two peptides that have an alanine at position A' of the peptide. The art teaches that alanine is one of the two residues normally expected at this position, and that substitution of serine (the other expected residue) with alanine does not prevent cleavage. See e.g., Urbani et al., J Biol Chem 272: 9204-09, at 9204 right column (teaching the (D/E)XXXXC(A/S) motif); and Zhang, supra, at 6210 (teaching that residue A', referred to as P1', can be replaced with alanine "with little effect"). Thus, it is clear both that the alanine is not the modification to these peptides conferring the uncleavable functionality, and that presence of proline in this position is not the only modification that results in uncleavability.

In the art of protein modification, it is accepted that the effect of any particular substitution on the function of a protein is unpredictable absent specific teachings relating the modified residue to the protein's structure and function. Bowie et al., Science, 247:1306-10, at 1306. However, Bowie also teaches that proteins are generally tolerant to substitutions. Id. This tolerance to modification has specifically been demonstrated with respect to peptide targets of the NS3 protease. For example, on page 7527, the Kolykhalov reference not only teaches the effect of the proline substitution, but also notes that other substitutions permitted efficient cleavage- and were therefore not inhibitory. Thus, these teachings, in combination of with the teachings of present application as described above, indicate that there is significant uncertainty

as to what peptide modifications can be made that will result in a peptide that is not cleavable by NS3.

In addition, it is noted that each of the disclosed species in the present application represent one of two general types of modified peptides; the first being a modified form of the NS5A/5B cleavage site, and the second being related to the NS4A/4B cleavage site. Cf, the sequences of Table 4 with the sequences of Table 1 in Zhang, page 6210. These peptides therefore do not represent the full scope of the peptides encompassed (structurally) by the claimed formulas. Further, the art discloses at least two peptides that fall within the claimed formulas, but are cleavable by the NS3 protease. See, SEQ ID NO: 29 of WO 97/08304 (identified on page 20 if the reference as a NS3 substrate), and peptide DEMEECAAHL of Table V in the Urbani reference. Additionally, the art also identifies at least two peptides that are not cleavable, but fall outside the scope of the claimed formula. See e.g., Urbani, supra (peptide DEMEEAASHL- comprising a serine at position B', and therefore not within the claimed formula); and Zhang, page 6210, Table 2 (peptide P1 Ala, comprising a tyrosine at position D'). Thus, there is evidence that the disclosed formulas themselves do not correlate to the uncleavable nature of the peptides. This is particularly the case when it is considered that each of the disclosed peptides that do fall within the scope of the claims on Table 4 of the present application comprise one of two residues in the A' position- one of the three required positions identified in the Urbani motif.

Further, in each of the two types of uncleavable peptides disclosed in the application, there is either a methylated or non-methylated aminobutyric acid (Abu) in position A of the peptide. The art indicates that Abu residue itself does not make a peptide uncleavable. See e.g.,

Landro et al., Biochem 36:9340-48 at 9343 (disclosing a cleavable variant of the NS5A/5B cleavage site comprising an Abu at position A). However, in peptide 3 of the application, there is no other modification to any of the three residues identified by the Urbani motif (representing the F, A, and A' positions in the claimed peptides). In view of this, it appears that the uncleavable nature of these peptides is due, at least in part, to the modification of a different amino acid from those identified in the cleavage motif identified in the art. The teachings thereby indicate that even knowledge in the art of the NS3 recognition motif is insufficient to establish certainty in effects of various modifications.

In view of these teachings, and the limited disclosure of operable species of elected peptides, there is no showing that demonstrates any correspondence between the provided peptide formulas and the functional limitation requiring that the peptides are not cleaved by NS3. Further, for the same reasons, and in view of the uncertainty in the art, the disclosed species are also insufficient support for the full scope of the claimed genus. The indicated claims are therefore rejected as lacking sufficient written description support to demonstrate possession of the full scope of the claimed genus of peptide.

6. Claims 1-12, 14, and 16-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus of peptides (or methods of using such for the treatment of an HCV infection) having the formula Pep-A'-B'-C'-D', wherein Pep is any

peptide or analog thereof that binds to HCV NS3 protease, and wherein the peptide is substantially uncleavable by NS3. Further, claims 11, 12, and 21 limit the peptides to embodiments wherein Pep comprises peptides according to the F-E-D-C-B-A formulas presented in (e.g.) claims 11 and 12. Thus, the claims are drawn to a genus of peptides comprising a Pep component that may be any peptide (or analog) that is capable of binding to NS3, and a subgenus thereof wherein the Pep component corresponds to the presented F-E-D-C-B-A formulas.

In addition, claim 10 is additionally drawn to embodiments wherein the Pep sequence is capable of binding to NS3, with an IC50 value of below 100μM, in the absence of the C-terminal A'-B'-C'-D' residues.

Grounds for finding support for a claimed genus have been described above (species disclosure, or teachings of function plus correlating structure). In addition to such disclosures, other factors may also be considered when making a determination as to whether a claimed invention has been adequately described. For example, the Federal Circuit has indicated that factors that may be considered are the knowledge in the particular field, the extent and content of the prior art, the maturity of the technology, and predictability of the aspect at issue. See e.g., *Capon v. Eshhar*, 76 U.S.P.Q. 2d 1078, at 1085 (CAFC 2005). Consideration of these factors in the present case does not support a finding that there is sufficient descriptive support for the full scope of the claimed genus.

With respect to peptides that are able to bind to NS3, the application provides a number of examples of such peptides. See e.g., Tables 2 and 3 (pages 14-17). However, these peptides do not represent the full scope of the peptides encompassed by the claims. In particular, the formulas presented in claims 11 and 12 permit many Pep sequences that are not represented in

the tables. Further, the tables also teach the efficacy of these disclosed peptides for the binding (inhibition) of NS3. They indicate that the efficacy of the peptides varies widely, and provides no basis for those skilled in the art to determine the effects of other modifications from those actually disclosed.

Further, there is nothing in the application to indicate that any peptide, no matter how derived, that falls within the scope of formulas presented in the claims would be able to bind to NS3. Each of the peptides disclosed in the application is identified in the art, or is structurally related to a peptide so identified, as a modified form of one of the three sequences that NS3 targets for cleavage in the HCV polyprotein. Cf., Tables 2 and 3 with the peptides of Ingallinella et al., Biochemistry 37: 8906-14, Tables 1 (page 8908), or 3-5 (pages 8910-11). However, even if it were assumed (for argument) that the claims were limited to the formula of claim 12, this still describes the structures of over 44 thousand peptides or analogs, most of which would not be structurally similar to the peptides of native HCV sequences. Thus, the claims broadly read on any peptide that may or may not be so related so long as they either bind to NS3, or bind to NS3 and fall within the scope of the indicated formulas, without providing any addition guidance as to what these other peptides may be.

In addition to the limited species and limited teachings regarding the relationship between the disclosed formulas and functions, the art provides many teachings that indicate substantial uncertainty in the field. As was described above, the teachings of the Bowie reference indicate that the functional results of a modification to a protein are closely tied to the relationship between the modified residues and the overall function and structure of the protein. Page 1306.

The reference therefore indicates that, without detailed teachings regarding such relationships, there is little predictability in the results of a given modification.

This unpredictability can be seen in the teachings of the present application and in the teachings of the prior art. With respect to the present application, it was noted above that the application discloses an inhibitory peptide 3 in Table 4 of the application which comprises each of the three primary residues identified in the recognition motif of Urbani. However, this peptide is nonetheless uncleavable, despite modifications only in secondary positions. The art also demonstrates similar uncertainty. For example, the Zhang reference (supra.) discloses in Table 2 (page 6210) one NS3 peptide (P3 Ala) with an alanine modification in the C position of the Pep sequence that was not cleaved, whereas Urbani discloses in Table V (page 9207) that the same modification in a different NS3 target sequence (DEMACHASHL) resulted in a peptide that was still cleavable. Thus, absent some specific teaching associating the provided formulas as whole with the required functions, those in the art would have little certainty as to which peptides encompassed thereby would actually meet the functional limitations.

In view of these teachings, the limited examples provided in the application, and the scope of the genus claimed, the application has not provided sufficient descriptive support to demonstrate possession the of a genus comprising every peptide that binds to NS3, or a genus comprising every peptide according to the indicated formulas that bind NS3.

With respect to the subgenus of claim 10, it is noted that the application provides several examples of peptides that meet this functional limitation. However, as with the peptides that bind NS3 more generally above, the scope of these species is limited in comparison to the genus being

claimed (any peptide that has this function). Neither the claims nor the application provide any structural or other non-functional feature that is common to all such peptides, and distinguishes them from peptides that do not fall within the scope of the claimed genus. Further, those in the art would, looking at the peptides of Tables 2 and 3, be faced with the same uncertainties described above in determining what, if any, other peptides meet this functional limitation. Thus, claim 10 is rejected both due to its dependency from claim 1, and in view of its additional functional requirement.

7. Claims 16 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting NS3 protease activity in vitro, does not reasonably provide enablement for methods of treating or preventing HCV or related conditions through the administration of the identified genus of peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed

most relevant should be considered. In the present case, the factors considered most relevant are the provision of working examples in the application, the amount of guidance or direction presented, the quantity of experimentation necessary, the state of the prior art, the predictability of the art, and the scope of the claims.

As indicated above, the claims are drawn to the use of any of the indicated peptides for the treatment or prevention of HCV infection or related conditions. The claims broadly cover a large genus of peptides corresponding to modified forms of various HCV NS3 cleavage domains. However, while the application shows that a number of these peptides are non-cleavable in vitro (see e.g., pages 26-32), there is no demonstration that any of these peptides was able to treat or prevent HCV infections in vivo.

With respect to the treatment or prevention of HCV or related conditions, it is noted that the art teachings that there is no preventative treatment for HCV, and that treatments for the viral infection are of limited efficacy. See e.g., Steinkühler et al., Curr Med Chem 8: 919-32, at page 919, right column. The reference continues to note several of the challenges faced by practitioners of the art. Id. Steinkühler does teach that the identification of inhibitors of the NS3 protease is a promising field for the discovery of new HCV therapeutics. Page 920. However, like the treatment of HCV in general, the reference teaches that, despite knowledge of the NS3 activity gained in recent years, the development of potent inhibitors of the protease remains "elusive." Pages 922, and 929-30. While the art is optimistic regarding the development of NS3 protease inhibitors, it indicates that more is required for such identification than for a demonstration of in vitro protease inhibition. In short, while there is great deal of information in the art, there has so far been little success in the development of operable anti-HCV therapeutics.

In addition to the limited success in identifying effective HCV inhibitors in general, it is also noted that the art indicates that peptides are of limited use as drugs. Steinkühler, page 928. The teachings in the art indicate that identification of NS3 inhibiting peptides is more a starting point for the development of non-peptidic drugs rather than an endpoint in the identification of anti-HCV therapeutics. See e.g., Steinkühler, pages 928-929; and Ingallinella et al., Biochemistry 41: 5483-92, esp. page 5489. From these teachings, it is also apparent that there is little certainty in the form that any operable therapeutic would take. The art therefore indicates that the present state of the art of anti-HCV NS3 inhibitors is relatively undeveloped and faces a great deal of unpredictability.

In view of this unpredictability and the relatively undeveloped state of the art, the limited guidance provided in the application, and the lack of any demonstration of an operative working example, the claims are rejected as exceeding the scope for which the application is enabling. It is suggested that the claims be amended to read on methods for the inhibition of HCV NS3 protease activity, rather than for the treatment or prevention of HCV infection.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 3, 4, 10, 11, 14, 16, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over the teachings of Urbani et al. (J Biol Chem 272: 9204-09) in view of the teachings of the teachings of Gibson et al. (U.S. 6,001,967) and Kolykhalov et al. (J Virol 68: 7525-33). These claims are drawn to a genus of peptides according to the formula F-E-D-C-B-A-A'-B'-C'-D' as described in claims 1 and 11. In addition to the structure, the claims also require that the peptide is not cleavable by the HCV NS3 protease. Claim 10 additionally requires that the portion of the peptide corresponding to the F-E-D-C-B-A sequence (Pep in claim 1) has an IC_{50} value of below 100μM. Claims 16 and 22 also read on methods for the inhibition of NS3 protease activity, or for the treatment of an HCV infection through administration of the peptide to a human or mammalian subject suffering from HCV infection.

Urbani teaches peptides corresponding to the NS4A/4B cleavage site targeted by the NS3 protease in the HCV polyprotein. See e.g., Tale V, page 9207. The Urbani reference indicates that the peptides disclosed therein would be useful for the study of NS3 substrate recognition for the design of substrate-based inhibitors of NS3. Page 9209, last full paragraph. It is noted that the art recognized the potential of NS3 inhibitors as potential HCV therapeutics. See e.g., Grakoui et al., J Virol 67: 2832-43, at 2840; and Steinkühler et al., Biochemistry 37: 8899-8905 at 8904. Among the substrate peptides identified by Urbani is one having the sequence DEMEECAAHL. This peptide falls within the structural scope of the claimed peptides (assuming that the proline of the A' position has been substituted as permitted by the claims). With respect to claim 3, it is noted that the peptides of Urbani are indicated as being acylated. However, the reference also teaches the majority of the identified peptides, including DEMEECAAHL, as substrates for the protease. (The one peptide that is not cleaved has a serine in position B', which is not permitted

by the claimed formula). Therefore, although the DEMEECAAHL peptide meets the structural limitations of the claims, it differs from the claimed peptides in that it is disclosed as being a substrate to NS3, and is therefore cleavable by the protease.

Kolykhalov teaches modifications of the NS4A/4B cleavage site. The reference performed a number of modifications to the peptides corresponding to the indicated cleavage site, and determined the effect of such modifications on the recognition and cleavage of the peptides by NS3. See e.g., page 7527, right column. From the modifications, the reference determined that modifications of the position corresponding to position A' in the present claims (P1' in the reference) such that a proline is substituted for the native alanine results in a peptide that is not cleaved by the NS3 protease. However, while the reference provides these teachings, the reference does not explicitly suggest why such modification should be performed on other NS3 substrate peptides.

Gibson provides teachings relating to a protease from the Herpes virus (HSV). Like the Urbani reference, this reference also suggests substrate-based inhibitors as therapeutics for infection by the target protease. Column 8, lines 10-28. The reference particularly identifies non-cleavable derivatives of the substrates as inhibitors of the viral protease (id., lines 11-12), and teaches that such derivatives are made through the modification of the peptides, and the cleaved bond, such that its cleavage is inhibited or totally blocked.

Thus, the teachings of Gibson, which relate to the targeting of a viral protease for therapeutic treatment of infection by the virus, provide both a suggestion and motivation for the making of non-cleavage substrates of a viral protease. In view of these teachings, and the suggestion in the Urbani reference for the making of HCV NS3 inhibitors, it would have been

obvious to those of ordinary skill in the art to modify the substrates of Urbani with at least the proline substitution described by Kolykhalov. Further, those of ordinary skill in the art would have had a reasonable expectation of success from such modifications in view of the demonstration by Kolykhalov that such modified peptides were not cleavable by NS3. Because the combined teachings of the art renders obvious the use of such peptides as inhibitors of HCV infection, the methods of claims 16 and 22 are also rendered obvious.

It is noted that claim 10 provides an additional functional limitation with respect to the IC_{50} value of the F-E-D-C-B-A (Pep) sequence of the claimed peptides. The peptides of Urbani comprise the corresponding sequence DEMEEC (or Asp-Glu-Met-Glu-Glu-Cys). This is one of the Pep sequences identified in Table 2 (page 14) of the present application, and is described in that Table as having an IC_{50} value of less than 100 μM. Thus, the peptides that would result from the combination of Urbani and Kolykhalov meet the limitations of claim 10.

The combined teachings of these references therefore render the claimed inventions obvious.

10. Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urbani, Kolykhalov, and Gibson as applied to claims 1, 4, 10, 11, 14, 16, and 22 above, and further in view of the teachings of Lawrence et al. (U.S. 5,639,726) and Sumner-Smith et al. (U.S. 5,646,120). These claims read on the peptides of claim 1, wherein the peptides are, respectively, C-terminally amidated or N-terminally acylated.

It is noted that the peptides of Urbani are indicated as being acylated. However, the reference does not teach the disclosed peptides for use in therapeutic applications. Nor do the

teachings of the other references suggest the modifications of claims 2 and 3. However, acylation and amidation of peptides is known in the art, including for peptides to be administered to humans. See e.g., Lawrence, column 12, lines 52-61. Such modification is also taught specifically with respect to peptide inhibitors of viral protein activity. See e.g., Sumner-Smith, columns 9(lines 6-35) and 14 (lines 9-20, and 41-45). The Lawrence reference specifically teaches that incorporation of such protecting groups in peptides results in peptides with increased pharmacological activity and solubility. Thus, it would have been obvious to those of ordinary skill in the art to have modified the substrate-based NS3 inhibitors suggested by the other reference so as to result in a peptide better adapted for pharmacological use. Those in the art would have had a reasonable expectation of success in such modifications in view of the teachings of Lawrence and Sumner-Smith, and particularly in view of the indication by Lawrence that such modification is commonly known in the art. Thus, the combined teachings of these references render the claimed inventions obvious.

Conclusion

11. No claims are allowed. The peptides of claim 23 appear to be allowable over the art. Claim 23 is objected to a dependent on a rejected claim.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Z. Lucas
Patent Examiner